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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

**NOTE FOR GUIDANCE ON
PROCEDURE FOR COMPETENT AUTHORITIES ON THE
UNDERTAKING OF PHARMACOVIGILANCE ACTIVITIES**

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Note: This revision was considered necessary in particular to reflect the recently agreed arrangements for the conduct of pharmacovigilance for medicinal products authorised through the Centralised Procedure and the Mutual Recognition Procedure. New developments in the field of information technology have also been taken into account.

**PROCEDURE FOR COMPETENT AUTHORITIES ON THE
UNDERTAKING OF PHARMACOVIGILANCE ACTIVITIES**

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1. INTRODUCTION & LEGAL BASIS

As described in Council Regulations No. 2309/93 (Articles 19-22), 540/95 and Directive 75/319/EEC as amended (Chapter Va Articles 29a to 29i) each Member State must establish a national pharmacovigilance system for the collection and evaluation of information on medicinal products with particular reference to Adverse Reactions. Furthermore, Member States should take all appropriate measures to a) encourage physicians and other healthcare professionals to report suspected adverse reactions to the competent authorities and b) oblige marketing authorisation holders to systematically collect information on risks related to their medical products and to transmit those to the competent authorities.

The requirements and procedures involved in such a system are described in this guideline, which relates to medicinal products authorised in the community (using either national, centralised or mutual recognition procedures) and covers collection and evaluation of all information useful in the surveillance of medicinal products. This guideline should be read in association with other relevant pharmacovigilance guidelines (i.e. Conduct of Pharmacovigilance for Centrally Authorised Products, Conduct of Pharmacovigilance for Products Authorised Through the Mutual Recognition Procedure, Crisis Management Plan Regarding Centrally Authorised Products for Human Use and Note for Guidance on Rapid Alert System).

2. ESTABLISHMENT OF A PHARMACOVIGILANCE SYSTEM

Each Member State should have in place a system of drug surveillance, (hereafter referred to as "a national pharmacovigilance centre") for receipt and evaluation of all pharmacovigilance data within that Member State. Furthermore this centre must be in a position to handle these pharmacovigilance data in a way which is compatible with the procedures undertaken in the other Member States and the European Agency for the Evaluation of Medicinal Products (hereafter referred to as the "Agency") in order that pertinent data may be transferred between the Member States and the Agency.

The Pharmacovigilance Working Party of the CPMP has been given a mandate to provide a forum for discussion, consensus development and co-ordination of pharmacovigilance issues at community level. Each Member State should ensure that it co-operates with the pharmacovigilance working party in order to fulfil its pharmacovigilance requirements at community level.

All Member States should co-operate with the WHO Collaborating Centre for International Drug Monitoring through their pharmacovigilance centre.

3. MANAGEMENT OF PHARMACOVIGILANCE DATA

This section deals with the following procedures:

1. Management of spontaneous reporting systems
2. Management of company derived pharmacovigilance data
3. Management of pharmacovigilance data from other sources
4. Procedures for communications and evaluation of pharmacovigilance issues within the EU

3.1 Spontaneous Reporting Systems

3.1.1 Introduction

Each Member State should have in place a system for the collection of spontaneous suspected adverse reaction reports from health care professionals (e.g. free postal or telephone system), and marketing authorisation holders (hereafter referred to as “MA holders”), see also 3.2. Each pharmacovigilance centre must liaise with the healthcare professionals to increase the awareness of the reporting system, stressing its importance and encouraging reporting (e.g. by the provision of an easy system of reporting and feedback after each report as appropriate).

Member States should interact with doctors and other healthcare professionals to ensure adequate reporting of adverse reactions to the competent authorities. To this end, it is desirable that each Member State should ensure the following:

- that reporting of adverse reactions to the designated centre is made as simple as possible.
- that all adverse reactions are acknowledged where appropriate and further information is forwarded as requested.
- that regular contact is maintained between the pharmacovigilance centre and healthcare professionals for example by:
 - the publishing of regular adverse reaction bulletins,
 - the sending of "Dear Doctor" letters, where appropriate, (either by the competent authority and/or the MA holder),
 - the provision of requested information on a one-to-one basis where possible.

3.1.2 General Principles of Spontaneous Reporting Systems

The following recommendations concern the spontaneous reporting systems procedure:

- A healthcare professional or marketing authorisation holder reports a suspected adverse drug reaction related to one or more medicinal products, to a national competent authority (pharmacovigilance centre). Reports are made in writing (e.g. using report forms), by telephone, electronically, or by any other approved way.
- Reports are collected and validated by the pharmacovigilance centre and are usually entered into a database. Serious reactions should be handled with the highest priority. The database is used to identify potential signals and analyse data in order to clarify risk factors, apparent changes in reporting profiles etc.
- Case reports must be made accessible to the Agency, to the competent authorities of other Member States, and to the concerned MA holders according to the criteria laid down in the Regulation and Directive, and described in the documents “Notice to Marketing Authorisation Holders, Conduct of Pharmacovigilance for Centrally Authorised Products and Conduct of Pharmacovigilance for Medicinal Products authorised through the Mutual Recognition Procedure”.

The following procedures relate to the competent authorities of Member States and are independent of the structure of the national pharmacovigilance system (centralised or regionalised). The procedures are divided into:

- case report collection and validation, case report storage,
- case report processing (evaluation and presentation for transmission), information feedback,
- Protection of data confidentiality and security,
 - data quality control and quality assurance.

3.1.3 Case Report Collection and Validation

This concerns the collection and validation of primary data i.e., the data transmitted from the reporter to the competent authority. For the validation and management of electronically transmitted reports, the specific operational procedure should be followed.

Case Report Collection

A pharmacovigilance spontaneous report concerns a single case; one patient, one identifiable reporter, one or more suspected reaction(s), and one or more suspect medicinal product(s). According to European Directives and Regulations, only serious cases reported by healthcare professionals will be received on an expedited basis.

Case Report Validation

If the initial report is oral or made by telephone, it should be confirmed in writing by a healthcare professional. When several suspected reactions to one or more suspected drugs occur in one patient, but are considered to be independent reactions, they should be treated as separate reports. If considered appropriate, especially in the case of serious or unexpected reactions, data in the report concerning the patient, the medicinal products taken, the reactions, including signs and symptoms and laboratory reports, and the dates should be confirmed by copies of most important and relevant original documents (e.g. hospital discharge forms, specialist reports, laboratory tests, prescriptions and post mortem reports etc.).

Completeness of reports should be evaluated according to data required, as set out in the Notice to Marketing Authorisation Holders (Volume 9 of Rules Governing Medicinal Products in The European Union) or formats for data transmission (see "Individual Case Presentation for Transmission" 3.1.5 below).

Incomplete reports, especially when concerning serious or unexpected reactions, should be followed up promptly by obtaining further information from initial reporter or other available sources. In some cases, it would also be appropriate to conduct further follow-up to obtain data on the long-term outcome of the reaction.

An adverse drug reaction report must contain the following information, as defined in the Notice to Marketing Authorisation Holders: an identifiable health-care professional, an identifiable patient, at least one suspected substance/medicinal product and at least one suspected reaction. This is the minimum information which allows the case to be entered onto a data base and become available for signal generation in order to facilitate evaluation of cases. Every effort should be made to obtain complete information where appropriate.

A reaction is suspected if either the reporting healthcare professional or the MA holder believes there is a possible causal relationship between it and the drug in question. If a reaction is spontaneously reported, this usually implies a positive judgment from the reporter unless the reporter explicitly gives a negative judgement on a causal relationship.

3.1.4 Case Report Storage

Initial raw data (paper based) must be stored and treated in the same way as other medical documents, with appropriate respect for confidentiality.

Case reports should be stored in a database by the pharmacovigilance centre. Data storage should ensure on-line accessibility of data at all reasonable times. Recommendations cover individual data entry, audit trail, and correct use of terminologies.

Data Entry

Conformity of stored data with the initial report should be ensured by a quality control procedure which provides for validation against the original data or images thereof.

Audit Trail

Storage should ensure traceability (audit trail) of all data entered or modified, including dates and sources of received data, dates and destinations of transmitted data.

Terminologies

The internationally agreed ICH medical terminology (MedDRA) should be used. Until MedDRA becomes available and its use widely implemented, the terminologies used to code diseases and adverse drug reactions should ensure compatibility of reports between Member States. Reports entered into a database should be coded according to internationally accepted terminologies, (MedDRA, WHOART, ICD 9, etc.) or with mutually accepted terms enabling connections with internationally accepted terminologies, which are compatible with MedDRA Version 2. Reaction terms should be entered as the closest term available in the terminology, and, if possible, also in the original reporter's words. Use of terminologies should be monitored and validated, either systematically or by regular random evaluation. Data entry staff should be instructed in the use of the terminologies, and their proficiency verified.

3.1.5 Case Report Processing: Evaluation of Seriousness/Expectedness and Presentation for Transmission

Case report processing concerns evaluation of data in individual cases, identification of individual cases requiring specific handling, recognition and processing of alerts, and any other data processing of aggregate cases.

Evaluation of Data in Individual Cases

Data evaluation includes validation of the case report and determination of seriousness, and of expectedness of the suspected reaction. These terms (seriousness & expectedness) have specific meanings in the context of ADR report evaluation (see definitions). Evaluation of the probability of the causal relationship between medicinal products and the suspected reaction(s) is undertaken when considered appropriate. All methods used to evaluate these parameters should be documented. Evaluators should be trained in the methods used and their training verified.

Management of Duplicate Reports

Some cases, especially those which are serious, will probably be reported to competent authorities from more than one source or from a single source through more than one channel. The competent authority should make every effort to ensure that case reports contain sufficient information to identify such duplicates, e.g. from patient / reporter initials (or names if allowed), addresses, date of birth, other dates. Databases should be reviewed regularly to identify duplicates in accordance with national competent authority and Agency procedures. After identification, duplicates should be flagged as such.

Identification of Individual Cases Requiring Specific Handling

Database management should ensure compliance with regulations, i.e. identification of cases flagged as serious or unexpected and of any other circumstance requiring specific handling or transmission. Procedures should be in place to ensure that cases previously identified and processed are identified as such and not processed or transmitted repeatedly as new cases (see audit trail 3.1.4 above).

Individual Case Presentation for Transmission

Cases sent to other competent authorities or MA holders should be transmitted according to the approved formats, as defined by European guidelines.

Aggregate Case Processing and Alert Identification

Database management should enable users to identify case aggregates or trends indicating a signal. Once a possible signal has been identified, the possibility of a causal relationship should be assessed. In these cases, all adverse drug reaction reports should be classified according to national preferences or requirements, using nationally or internationally accepted methodologies. All reports fulfilling the minimum information requirement must be included in the overall analysis. Certain analyses (for example those concerning the role of risk factors) may be confined to cases where enough information is available, but it should be made clear that this is a subset of the data.

Aggregate case processing should allow case grouping by accepted terms (see Terminologies 3.1.4 above). The terminology used for case aggregation should be specified.

Competent authorities and MA holders should inform each other of identified signals which may impact on the risk-benefit profile of the medicinal product. The rapid alert should be used by competent authorities when applicable.

3.1.6 Information

Competent authorities should ensure that the reporter(s) of a case is informed of its receipt and provided with the allocated reference number if appropriate, and additional information, if requested.

Competent authorities should ensure that ADR data are transmitted to the MA holder as required.

Competent authorities should also ensure that healthcare professionals (and when necessary, treated patients) are informed of any significant changes where appropriate in the medicinal product information (SPC) and of any suspected hazards requiring vigilance.

Competent authorities should ensure that proper and timely information is provided to international bodies, in particular the World Health Organisation (WHO), in accordance with the guideline “Principles of Providing the World Health Organisation with Pharmacovigilance Information (CPMP/PhVWP/053/98)”.

3.1.7 Quality Control and Quality Assurance

Quality control and quality assurance concern every step in the processes described above. Quality control and quality assurance should be ensured by competent authorities, which should devise and implement the necessary procedures.

3.1.8 Confidentiality and Security

Confidentiality of patients' records including their personal identity, if given, should always be maintained; where possible, identifiable personal details of reporting healthcare professionals should be kept in confidence, as appropriate and in keeping with national & European legislation.

At each stage of storage and processing of pharmacovigilance data, all care must be taken to ensure data security and confidentiality. This involves strict control of access to documents and to databases to authorised personnel sharing the medical and administrative confidentiality of

the data. This security extends to the complete data path. Case report information should only be provided in an anonymous form.

In addition, procedures should be taken to ensure security and noncorruption of data during data transfers.

3.2 Company Derived Pharmacovigilance Data

Introduction

According to the aforementioned legislation, the person responsible for placing any medicinal product on the market must ensure that he has an appropriate system of pharmacovigilance in place in order to ensure responsibility and liability for his product on the market and to ensure that appropriate action can be taken, when necessary. Guidance for MA holders on the implementation and practical procedures involved in complying with this legislation is laid out in the Notice to Marketing Authorisation Holders.

Company derived pharmacovigilance will be in one of the following formats;

1. Adverse reaction case reports
2. Periodic safety update reports
3. Company sponsored post-authorisation safety studies.

This section deals with the procedures, to be undertaken by the pharmacovigilance centre, for handling company-derived pharmacovigilance data.

3.2.1 Adverse Reaction Case Reports

Each pharmacovigilance centre should ensure that all reports submitted by the MA holder conform with the requirements as laid out in the Notice to Marketing Authorisation holders, in order to ensure conformity of reporting of adverse reactions by MA holders in each Member State. Furthermore, each pharmacovigilance centre must ensure the validation and verification of all data included in these case reports as far as possible. Finally, each centre should ensure that these reports are followed up by the MA holder where appropriate, in order to improve the quality of data available and to facilitate causality assessment. Competent authorities should ensure that they have the capability to send and receive ADR reports electronically and to encourage MA holders to do so in a defined format.

3.2.2 Periodic Safety Update Reports

A periodic safety update report is intended to provide an update of the world-wide safety experience of a medicinal product to competent authorities at defined times post-authorisation. It is the responsibility of each pharmacovigilance centre to evaluate these reports for nationally authorised products as well as products authorised via the mutual recognition procedure, as appropriate. For practical reasons, PSURs for products authorised via the mutual recognition procedure are evaluated by the Reference Member State (RMS). An assessment report is circulated by the RMS to all Member States (CMS) within 6 weeks of receipt of the PSUR. In the case of nationally authorised products, any major action (eg variation, suspension or withdrawal of a marketing authorisation) considered necessary as a result of such evaluation should be notified to the Agency and the other Member States according to established procedures. Periodic safety update reports for centrally authorised products are evaluated by the rapporteur according to a timetable agreed by the CPMP. (See 3.4.4 below for procedures for medicinal products, authorised via the Centralised or Mutual Recognition Procedures).

3.2.3 Company Sponsored Post-Authorisation Safety Studies

These studies are normally conducted to assess the clinical safety of marketed medicines in routine clinical practice; they may be either hypothesis-generating or hypothesis-testing. MA holders proposing to perform such studies have been advised to discuss the draft protocol with the relevant regulatory authorities (see Notice to Marketing Authorisation Holders) (National legislative requirements or guidelines will have been taken into account in those Member States where these exist).

The pharmacovigilance centre may review studies, which are taking place within its jurisdiction on a regular basis. All serious adverse reactions, resulting from these studies, should be submitted in the usual way by the MA holder/investigator and should be dealt with as outlined below.

On completion of each study, the final report should be evaluated and, in the case of nationally authorised medicinal products, all relevant data (e.g. showing significant changes in the frequency of known adverse reactions, the development of unexpected adverse reactions, new interactions etc.) should be incorporated into the Summary of Product Characteristics (SPC) and notified to the other EU Member States and the Agency. (See 3.4.3 below for procedures for medicinal products, authorised via the Centralised or Mutual Recognition procedures).

3.2.4 Competent authorities should ensure that they communicate with MA holders according to existing legislation and guidelines (Directive 75/319 as amended, Council Regulation 2309/93, Note for Guidance on Rapid Alert System).

3.3 Pharmacovigilance Data from Other Sources

3.3.1 Intensive Monitoring Schemes

Intensive Monitoring is defined as a system of record collation in designated areas e.g. hospital units or by specific physicians in community practice. The competent authority may be involved in the drawing up of the protocol to undertake this collection of data or will be informed that such monitoring is taking place.

Furthermore, it may be considered appropriate in the authorisation of certain medicinal products to impose specific requirements in respect of reporting serious or unexpected reactions on the prescribing physician and to make these requirements a condition of use of the product under the terms of the marketing authorisation.

The relevant pharmacovigilance centre should ensure that data and reports are collected at agreed intervals and in an appropriate format.

3.3.2 Data on Misuse/Abuse of Drugs

Reports of suspected adverse reactions due to misuse and abuse of medicinal products (associated with therapeutic use), which are received by the pharmacovigilance centres (via spontaneous reports, company reports etc.) should be handled in the same way as for the other types of reactions.

3.3.3 Other Pharmacovigilance Data

These data include drug usage figures, published adverse reaction reports, pharmacoepidemiology studies conducted by organisations other than the MA holders, pre-clinical studies or significant quality data and reports on products not currently marketed in the Member States. These are important for determining frequency, occurrence of unexpected adverse reactions, new interactions etc. and overall risk/benefit analysis. In those cases (e.g.

from pharmacoepidemiology studies) where significant data are received from these sources, these findings may be transmitted to the other Member States and the Agency, as part of a routine exchange of pharmacovigilance information, with a view to taking action as appropriate (see also Section 3.4.2).

3.4 Procedures for Communications and Evaluation of Pharmacovigilance Issues in the EU

Introduction

This section describes the procedures that should be implemented in order to improve the communication of pharmacovigilance information within the EU and to optimise human resources for identifying and evaluating pharmacovigilance signals.

The following areas will be discussed:

1. Transmission of Serious and other Adverse Reaction reports - general principles.
2. Procedures for transmission and management of detected signals.
3. Procedures for the final report evaluation of company sponsored post authorisation safety studies.
4. Procedures for the Evaluation of Periodic Safety Update Reports.
5. Special Safety Monitoring of Medicinal Products.
6. Technologies on data transmission to facilitate the implementation of the procedures conforming the new European Pharmacovigilance System.

3.4.1 Transmission of Serious Adverse Reaction Reports

All serious suspected reactions, occurring within the Member State and notified to the pharmacovigilance centre should be transmitted, according to the aforementioned legislation, to the MA holder and in the case of centrally authorised products to the Agency within 15 days of their receipt by the pharmacovigilance centre. In the case of centrally authorised medicinal products, it is the responsibility of the Agency to inform each Member State of serious reports received from other Member States. The method of transfer of information to be used should be such as to ensure that the information is transmitted within the time frame outlined in the document "Conduct of Pharmacovigilance for Centrally Authorised Products". The data transmitted should be as complete as possible in order to facilitate assessment but it is not obligatory on the pharmacovigilance centre to have made a formal evaluation before this transmission. (See Rapid Alert 3.4.2 below).

Transmission of Other Adverse Reaction Reports

These include non-serious expected or unexpected adverse reaction reports which are received from all sources. Whenever appropriate, these data should be available for transmission, in summary form, to all relevant parties (MA holder, Member States, Agency), as outlined below (See 3.4.2, "Non-urgent Exchange of Pharmacovigilance Information"). Only data, evaluated by the pharmacovigilance centre are considered for transmission here.

3.4.2 Procedures for Transmission and Management of Detected Signals

Once a potentially serious safety problem (e.g. a series of unexpected or serious ADRs or an increase in the reporting rate of a known ADR report) for a certain product has been detected by a National Pharmacovigilance Centre, it should be transmitted to the other Member States and the Agency.

It is essential that there is communication of the problem at an early stage, before a national decision is taken.

There are two ways for communicating this kind of information, i.e. rapid alert and non-urgent exchange of information.

Rapid Alert

The purpose of the Rapid Alert System is to inform with the appropriate degree of urgency, the other Member States, the European Commission and the Agency on pharmacovigilance data of medicinal products. Each Member State is normally responsible for contacting the MA holder(s) in its Member State, when appropriate. Rapid Alerts concerning batch problems are not considered in these guidelines.

The criteria for sending a rapid alert is the concern about a change in the balance between risks and benefits that could lead to major changes in the authorisation such as urgent suspension or withdrawal of the marketing authorisation, the introduction of major contraindications, restrictions in the indications or availability of a product.

This should also include any such action initiated by the MA holder. See Note for Guidance on Rapid Alert System (RAS) in Pharmacovigilance (CPMP/PhVWP/005/96)

Non-urgent Exchange of Pharmacovigilance information

The criteria for a non-urgent exchange of pharmacovigilance information are:

- Requests for information from Member States, The European Commission and the Agency which may relate to a variety of safety issues which may require non-urgent actions or minor changes in the SPC.
- Provision of information between involved parties which does not require any response.

Prior to circulation of such information Member States who consider a pharmacovigilance hazard should liaise with the Reference Member State in the case of product authorised via the Mutual Recognition Procedure or with the rapporteur and the Agency in the case of centrally authorised products.

Electronic transmission using the template available on the EudraNet homepage will be the preferred mode of information exchange. It is important that this exchange of pharmacovigilance information is focused on important issues so that involved parties do not become overloaded with information.

The procedure to be followed in this exchange of pharmacovigilance information is as follows:

- The information should be clearly labelled as non-urgent exchange of pharmacovigilance information.
- The reason for sending the information should be clearly stated.
- Any information required of recipients should be specified clearly.
- Responses should only be sent to the originator of the request and the Agency.
- The originator of the request should collate the information received and send this to all Member States, only if the originator of the request wishes the issue to be considered at the pharmacovigilance working party. See Note for Guidance on Rapid Alert System (RAS) in Pharmacovigilance (CPMP/PhVWP/005/96)

3.4.3 Procedures for the Final Report Evaluation of Company-sponsored Postauthorisation Safety Studies

In accordance with the Guidelines for marketing authorisation holders on company-sponsored post-authorisation safety studies (Notice to Marketing Authorisation Holder), a final study report has to be sent by the MA Holder to the relevant Member States and in the case of centrally authorised products to the Agency.

In the case of studies conducted for nationally authorised medicinal products the relevant Member State(s) should be responsible for the evaluation of the final report.

In case of medicinal products nationally authorised in several countries through the Mutual Recognition Procedure, and in order to optimise human resources, evaluation of the final report will normally be carried out by the Reference Member State.

In case of medicinal products authorised through the Centralised Procedure, the Rapporteur who evaluated the product for its registration will normally assess the final report. A co-rapporteur may also be appointed by the CPMP.

All data from the study have to be evaluated and an assessment report will be elaborated as a result. This report has to be distributed among Member States/CPMP/Agency, as appropriate within three months of receipt of the formal report from the MA holder.

If any pharmacovigilance issue demanding an action is identified in any phase of the evaluation, it will be communicated using the appropriate procedure as described above (3.4.2), including at least the minimal data (Annex III) and the assessment report (Annex II).

3.4.4 Procedures For the Evaluation of Periodic Safety Update Reports

In accordance with the legislation, each Member State and the Agency will receive regular safety update reports from the MA holder.

In the case of medicinal products nationally authorised in several countries through the Mutual Recognition Procedure and with the aim of optimising efforts, the evaluation of these updates will normally be carried out by the Reference Member State within the agreed timetable outlined in the document “Conduct of Pharmacovigilance for Products Authorised through the Mutual Recognition Procedure”.

In the case of medicinal products authorised through the Centralised Procedure the Rapporteur who evaluated the product for its registration will normally assess the Safety Update Reports within the agreed timetable described in the document “Conduct of Pharmacovigilance for Centrally Authorised Products”.

An assessment report will be elaborated and distributed by the Reference Member State to all Member State(s) within six weeks of receipt of the PSUR for medicinal products authorised via the mutual recognition procedure; or by the rapporteur to all Member States and the Agency according to the timetable adopted by the CPMP for medicinal products authorised via the Centralised Procedure.

3.4.5 Technologies on Data Transmission to Facilitate the Implementation of the Procedures Conforming the European Pharmacovigilance System

Compliance with the Directives and the development of the European Pharmacovigilance system has resulted in the development of a network (EudraNet) which enables electronic data transmission.

Standardisation of data elements for the electronic transmission of individual case safety reports (ICHE2B) have been agreed. The agreed (ICH M2) standardised electronic

transmission format (SGML) will facilitate automatic data transfer between national databases, the Agency and the pharmaceutical industry as appropriate.

At this stage, four different levels of information can be identified:

1. Transmission of simple messages and free text document. This will cover the exchange of assessment reports (e.g. Annex I for drug safety problem assessment), meeting announcement and routine contacts between National Administrations, the Commission and the Agency.
2. Exchange of aggregate information such as the one described for the Rapid Alert and Non-urgent Exchange of Pharmacovigilance Information (Annex III).
3. Exchange of cumulative information (Annex III).
4. Exchange of single case data, via EudraWatch that will enable expansion of the information whenever needed and the compliance with the Directives using one unique transmission formats irrespective of the recipient system.

Apart from the facilities expressed, the electronic connection among every Member State and between Member States and the Agency provides other benefits such as automatic acknowledgement of when the information has arrived and of when this has been read by any of the recipients.

EudraNet provides all features of electronic transmission of information and security to ensure, if and when required, confidentiality, integrity, authentication and non-repudiation of the message

According to the functional aspects of exchange of information via EudraNet are described in the Standard Operating Procedures “EudraNet E-Mail Policy” (IT-SOP 972.2.8) and “EudraNet Network Policy” (IT-SOP 9720.3.2), Member States are required to use their electronic mail boxes:

- functional addresses: pharmacovigilance, information, RA
- working group addresses: EudraWatch

4. CHANGES TO MARKETING AUTHORISATION

The competent authority in each Member State as part of its obligation to undertake ongoing evaluation of benefit/risk assessment must ensure that all pharmacovigilance data received and evaluated, as outlined above, are taken into account on an ongoing basis

In the case of nationally authorised medicinal products, where updated pharmacovigilance data are seen to adversely effect the benefit/risk profile of the medicinal product, the competent authority may wish to vary/withdraw the Marketing Authorisation or not to renew it as appropriate. Any significant change to the MA status or SPC, undertaken nationally as a result of these pharmacovigilance data should be notified to the other Member States and the Agency.

The procedure to be followed for changes to MA status or SPC of medicinal products, authorised via the Mutual Recognition procedure is laid out in Commission Regulation EC 541/95 and the document on Pharmacovigilance for Mutually Recognised Products. It is the responsibility of the Reference Member State to co-ordinate the procedure. The changes are implemented simultaneously in all concerned Member States.

In the case of centrally authorised medicinal products, changes in the SPC or MA status are undertaken according to Commission Regulation EC 542/95 and as outlined in the document, Conduct of Pharmacovigilance for Centrally Authorised Products.

As described in Council Regulations 541/95 & 542/95, the MA holder may take provisional urgent safety restrictions in the event of risk to public health. These must be notified to the Agency and the Rapporteur (in the case of centrally authorised products) or the relevant competent authorities (in the case of products authorised in the mutual recognition procedure) within 24 hours before implementation. The Agency and national authorities have an opportunity to comment. The changes must be submitted as type II variations as quickly as possible after implementation. An urgent safety restriction for centrally authorised products may also be initiated by the European Commission.

Under the terms of Articles 12, 15a & 15b of Directive 75/319/EEC, as amended, and Article 18 of Council Regulation (EEC) 2309/93, a Member State, the Commission or MA holder may refer a pharmacovigilance matter to the CPMP whenever the interests of the Community are involved. With respect to Articles 12, 15a & 15b, the procedure to be followed is laid down in Article 13 of Directive 75/319/EEC as amended.

These matters may be referred to the pharmacovigilance working party for consideration by the CPMP. The final decision reached will be binding on all concerned Member States.